

CORRECTED VERSION

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 July 2002 (04.07.2002)

PCT

(10) International Publication Number  
**WO 02/051385 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 9/14**

(21) International Application Number: **PCT/EP01/14967**

(22) International Filing Date:  
18 December 2001 (18.12.2001)

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:  
**MI2000A002803**  
22 December 2000 (22.12.2000) **IT**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **NICOX S.A.** [FR/FR]; 2455, routes des Dolines, Espace Gaia II - Bâtiment I, F-06906 Sophia Antipolis Cedex (FR).

Published:  
— *with international search report*

(48) Date of publication of this corrected version:  
31 October 2002

(72) Inventors; and  
(75) Inventors/Applicants (*for US only*): **TRESPIDI, Laura** [IT/IT]; Via Lungo Adda, I-26026 Pizzighettone (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(15) Information about Correction:  
see PCT Gazette No. 44/2002 of 31 October 2002, Section II

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso dei Porta Vittoria, 9, I-20122 Milano (IT).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES**

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.



WO 02/051385 A1

USSN 10/828,419

PC25684A

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 July 2002 (04.07.2002)

PCT

(10) International Publication Number  
**WO 02/051385 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 9/14**
- (21) International Application Number: **PCT/EP01/14967**
- (22) International Filing Date:  
18 December 2001 (18.12.2001)
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:  
**MI2000A002803**  
22 December 2000 (22.12.2000) **IT**
- (71) Applicant (*for all designated States except US*): **NICOX S.A.** [FR/FR]; 2455, route des Dolines, Espace Gaia II - Bâtiment I, F-06906 Sophia Antipolis Cedex (FR).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **TRESPIDI, Laura** [IT/IT]; Via Lungo Adda, 56, I-26026 Pizzighettone (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).
- (74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso dei Porta Vittoria, 9, I-20122 Milano (IT).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- *with international search report*
  - *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES**

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.

**WO 02/051385 A1**

**Solid dispersions of nitrate active principles****FIELD OF THE INVENTION**

The present invention relates to solid dispersions of nitrate active principles characterized by an increased dissolution rate and/or apparent solubility of said active principles and to a method for their production.

**STATE OF THE ART**

The applicant has developed a number of active principles, characterized by the presence in their structure of a nitro group, having remarkably advantageous pharmacological properties. These active principles are described in the patents: EP670825, EP722434, EP759899, EP609415, US5703073, and in the patent applications WO98/15568, WO98/21193, WO00/51988, WO00/61537, WO00/61541, WO00/61604, WO00/25776, MI99A001817.

Unfortunately, the utility of many of the above mentioned active ingredients is limited by their scarce solubility in water, which results in an insufficient and irregular absorption and a slow onset of the pharmacological action. This last aspect is particularly problematic in case of active ingredients such as, for instance, anti-inflammatory active ingredients and/or analgesics for which a rapid onset of the therapeutic action is of fundamental importance.

Thus, there is a need to develop new pharmaceutical formulations for the administration of nitrate active principles which, compared with traditional formulations, are characterized by an improved bioavailability and a faster onset of action. It is known that the dissolution rate of poor water-soluble drugs can be increased by their conversion to the corresponding amorphous forms. A technique which can be used to this purpose is the formation of a solid dispersion of the active agent in an inert matrix, usually of polymeric nature. Nevertheless, this technique does not always allow to obtain the amorphous form and consequently the increase in dissolution rate of the active agent. Several parameters such as, for instance the interactions between the polymer and the active ingredient, the ratio between them and the production technique adopted influence the chemical-physical features of the solid dispersion obtained. Thus, for each particular active ingredient it is necessary to select both the polymer and the operative conditions for the preparation of the dispersion that lead to the conversion to the amorphous form.

## SUMMARY OF THE INVENTION

The inventors have now found that it is possible to obtain an increase in the dissolution rate and/or the apparent solubility and consequently in the bioavailability of nitrate active principles by forming solid dispersions of said active principles characterized in that the inert matrix includes at least one polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

Therefore, the present invention refers to solid dispersions comprising at least one nitrate active principle and a hydrophilic polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

## DESCRIPTION OF THE FIGURES

Figures 1, 2 and 3 show the thermograms of the crystalline form and of the amorphous solid dispersion according to the present invention of the following derivatives:

4- acetylaminophenyl ester of 4 nitroxybutanoic acid (NCX701)

2- (acetyloxy-benzoic-acid-3-nitroxymethyl) phenyl ester (NCX 4016)

(hydroxycortisone 21-[(4' nitroxymethyl)benzoate] (NCX 1022)

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to solid dispersions comprising at least one nitrate active ingredient and a hydrophilic polymer chosen among polyvinyl pyrrolidone, preferably having a molecular weight comprised between that of the polyvinyl pyrrolidone K17 and that of polyvinylpyrrolidone K30, cellulose ethers and polyethylene glycol, preferably having a molecular weight higher than that of PEG 1000, and more preferably PEG with a molecular weight higher than that of PEG 1500 and lower than that of PEG 6000. Among the cellulose ethers particularly preferred is the hydroxypropylmethylcellulose, preferably having a viscosity at 20°C, in a 2% aqueous solution, lower than 50 cPs, and preferably hydroxypropylmethylcellulose with viscosity comprised between 5 and 50 cPs.

By "nitrate active principles" it is meant compounds having formula (I).



wherein:

**p** is an integer equal to 1 or 0;

**q** is an integer equal to 1 or 2;

$A=R-T_1-$ , wherein  $R$  is the radical of a pro-drug having formula  $R-T_1-Z$ , chosen among the therapeutic classes of drugs reported here after, wherein

$Z$  is  $H$ ,  $OH$ ,  $NH_2$ ,  $NHR_3$ ,  $N(R_3)_2$ , wherein  $R_3$  is a linear or branched  $C_1-C_5$  alkyl radical

- 5  $T_1 = (CO)_t$  or  $(X)_{t'}$ , wherein  $X$  = an oxygen atom, a sulphur atom or  $NR_2$  wherein  $R_2$  is hydrogen or a linear or branched alkyl, having from 1 to 5 carbon atoms,  $t$  and  $t'$  are integer and equal to zero or 1, provided that  $t = 1$  when  $t' = 0$ ;  $t = 0$  when  $t' = 1$ ;

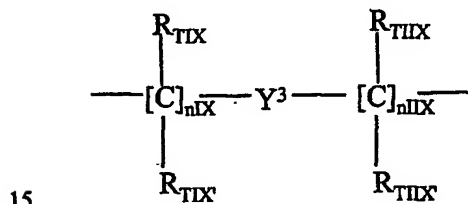
$X_1 = -T_B-Y-T_{BI}$  wherein  $T_B$  and  $T_{BI}$  are the same or different

- 10  $T_B = (CO)$  when  $t = 0$ ,  $T_B = X$  when  $t' = 0$ , being  $X$  as above defined;

$T_{BI} = (CO)_{tx}$  or  $(X)_{txx}$  wherein  $tx$  and  $txx$  are 0 or 1; with the proviso that  $tx = 1$  when  $txx = 0$ ;  $tx = 0$  when  $txx = 1$ ;  $X$  is as above defined;

$Y$  is a bivalent bridging group chosen among the following:

1)



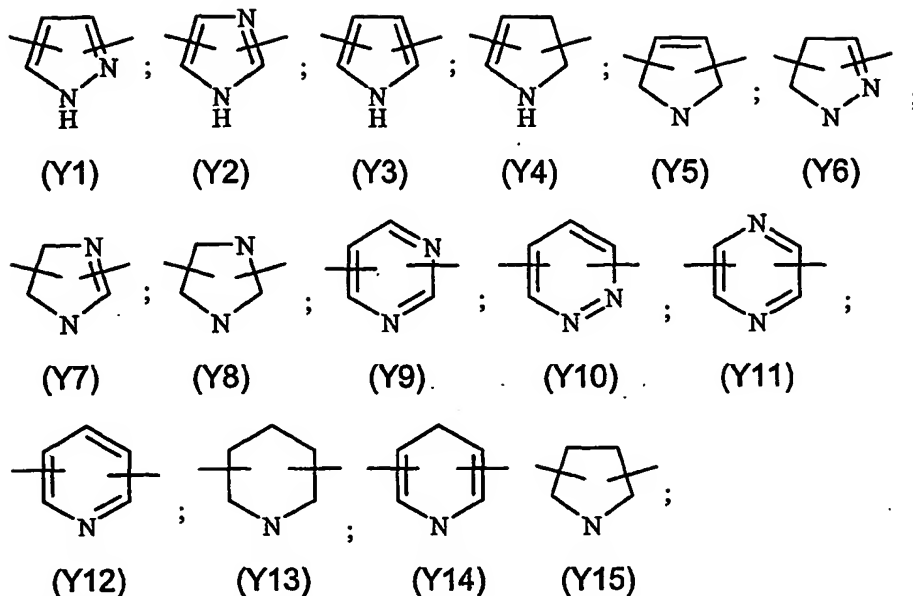
wherein:

$nIX$  is an integer comprised between 0 and 3, preferably 1;

$nIIX$  is an integer comprised between 1 and 3, preferably 1;

- 20  $R_{TIX}$ ,  $R_{TIX'}$ ,  $R_{TIIX}$ ,  $R_{TIIX'}$ , equal or different from one another, are  $H$  or linear or branched  $C_1-C_4$  alkyl; preferably  $R_{TIX}$ ,  $R_{TIX'}$ ,  $R_{TIIX}$ ,  $R_{TIIX'}$  are  $H$ .

$Y^3$  is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms and containing one or two nitrogen atoms,  $Y^3$  is preferably chosen among the following bivalent radical:

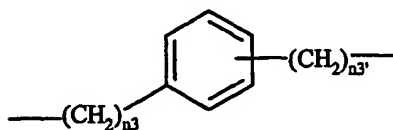


wherein (Y12) is preferred ;

2) an alkylene group R' wherein R' is C<sub>1</sub>-C<sub>20</sub> linear or branched when possible,  
 10 having preferably 2 to 6 carbon atoms, optionally substituted with at least one of  
 the following groups: -NH<sub>2</sub>, -OH or -NHCOR<sub>3</sub>, wherein R<sub>3</sub> is a linear or branched  
 C<sub>1-5</sub> alkyl;

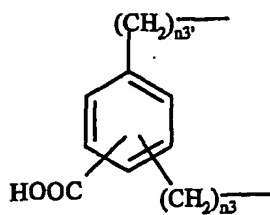
3) a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with  
 side chains R', wherein R' is as defined above, and at least one carbon atom of  
 15 the cycloalkylenic ring can be optionally substituted with etheroatoms.

4)



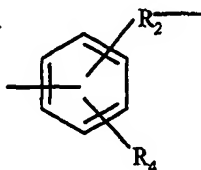
wherein n<sub>3</sub> is an integer from 0 to 3 and n<sub>3'</sub> is an integer from 1 to 3;

5)



wherein  $n_3$  and  $n_3'$  have the above indicated meaning,

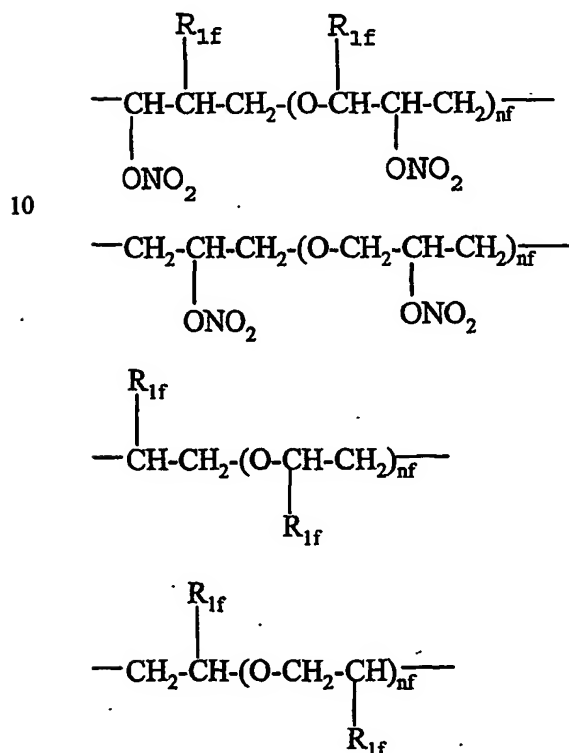
6)



wherein

- 5  $R_4$  is hydroxy, hydrogen, alkoxy  $R_5O-$  wherein  $R_5$  is a linear, branched or cyclic  $C_{1-10}$  alkyl group, preferably  $R_5$  is a methyl group;  
 $R_2$  is a linear or branched  $C_2-C_{10}$  alkenyl group, including at least one double bond, preferably  $R_2$  is the ethenylene group  $(-CH=CH-)$ ;

7)



wherein  $R_{1f} = H, CH_3$  and  $nf$  is an integer from 0 to 6; preferably from 1 to 4;

- 15 8) or Y is the bivalent radical whose precursor  $Z-T_B-Y-T_{BI}-Z$ , wherein Z is as defined above and it is chosen among the following compounds:  
 aspartic acid, histidine, 5-hydroxytryptophan, 2-thiouracil, 2-mercaptoethanol, hesperidine, secalcipherol, 1- $\alpha$ -OH-Vitamin D<sub>2</sub>, flocalcitriol, 22-oxacalcitriol, 24,28-

methylen-1 $\alpha$ -hydroxyvitamin D<sub>2</sub>, succinic acid, L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione, gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, hydrocaffeic acid, p-coumaric acid, vanillic acid, chlorogenic acid, kynureic acid, 5 siringic acid, nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfuretin, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydrohydroxyquinone, propyl gallate, saccharose, 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate, allopurinol, conyferyl alcohol, 4-hydroxyphenethyl alcohol, p-coumaric alcohol, curcumin, N,N'-diphenyl-p-phenylenediamine, thionine, hydroxyurea, 3,3'-thiodipronic acid, fumaric acid, di-10 hydroxymaleic acid, N-methylendiethanolamine, thiodiethylenglycol, 1,4-dioxane-2,6-dimethane, tetrahydropyran-2,6-di-methanol, 4H-pyran-2,6-di-methanol, cyclohexene-1,5-dimethanol, 1,4-dithian-2,6-dimethanol, thiophene-2,5-di-methanol, oxazole-2,5-di-methanol.

15 L= covalent bond, or L = X, X being as defined above, L = (CO)

W = Y<sub>T</sub>-X- wherein Y<sub>T</sub> has the same meanings of Y, but is different from Y,

R-T<sub>1</sub>-Z is chosen among the following drugs:

- Non steroidal anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, alclofenac, alminoprofen, amfenac, ampiroxicam, balsalazide, bendazac, 20 bermoprofen,  $\alpha$ -bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac, CS-670, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, 25 indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lomoxicam, loxoprofen, mechlufenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxifenbutazone, parsalmide, pemedolac, perisoxal, phenyl acetylsalicylate, pirazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamido-O-acetic acid, salicylsulfuric acid, salsalate, sulindac, suprofen, 30 suxibuzone, tenidap, tenoxicam, thiaprofenic acid, thiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepi-



rac, tomoxiprol,

Analgesics: paracetamol, acetaminosalol, aminochlorthenoxazin, acetylsalicylic acid, 2-amino-4-picoline, acetylsalicylsalicylic acid, anileridine, benoxaprofen, benzylmorphine, 5-bromosalicylic acid acetate, bucin, buprenorfine, butor-  
5 fanol, capsaicin, cincofenol, ciramadol, clometacine, clonixin, codeine, deso-  
morphine, dezocine, dihydrocodeine, dihydromorphine, dimefeptanol, dipyro-  
cetyl, eptazocine, etoxazen, ethylmorphine, eugenol, floctafenine, fosfosal,  
glafenine, hydrocodon, hydromorone, hydroxypetidine, ibufenac, p-la-  
ctophenetide, levorfanol, meptazinol, metazocine, metopon, morphine, nalbu-  
10 phine, nicomorphine, norlevorfanol, normorphine, oxycodone, oxymorphon,  
pentazocine, fenazocine, fenocoll, fenoperidine, fenilbutazone, phenylsalicylate,  
phenilramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

- Steroids: chenodeoxycholic acid, ursodeoxycholic acid, alclomethasone, al-  
gestone, amcinonide, beclomethasone, betamethasone, budesonide, chlor-  
15 prednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosteron,  
cortisone, cortivazol, deflazacort, desonide, desoximethasone, dexameth-  
asone, diflorasone, diflucortolone, difluprednate, estradiol, ethynilestradiol,  
fluazacort, flucoronide, flucortyn butyl, flumethasone, flunisolide, fluocinolone  
acetone, fluocinonide, fluocortolone, fluorometholone, fluperolone acetate,  
20 fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate,  
formocortal, halcinonide, halobetasol propionate, halomethasone, halopredone  
acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone,  
medrysone, meprednisone, mestranol, metilprednisolone, mitatrienediol,  
mometasone furoate, moxestrol, paramethasone, prednicarbate, prednisolone,  
25 prednisolone 25-diethylaminoacetate, prednisone, prednival, prednylidene,  
rimexolone, 21-acetoxy-pregnenolone, triamcinolone hexacetone, triamcino-  
lone acetone, triamcinolone, tixocortol;

- Bronchodilatory drugs: acephilline, albuterol, bambuterol, bamiphylline, bevo-  
nium methyl sulfate, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxeted-  
30 rine, diphylline, ephedrine, epinephrine, eprozinol, etaphedrine, ethylnorepi-  
nephrine, etophylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium  
bromide, isoetarine, isoprotenerol, mabuterol, metaprotenerol, oxitropium bro-

mide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-theobromoacetic acid, thiotropium bromide, tretoquinolol, tulobuterol, oxybutinyn, zaprinast.

- Expectorants and mucolytic agents: ambroxol, bromexine, domiodol, erdosteine, guaiacol, guaifenesine, glycerol iodurate, letosteine, mesna, sobrerol, stepronin, terpin, thiopronin;
- Anti-asthmatic, antiallergic and antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, hystamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplastat tosylate, terfenadine, tiaramide, bromexine, formoterol;
- ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naftopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;
- $\beta$ -blockers: acebutolol, alprenolol, amosulalol; arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol; carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronetalol, propranolol, sotalolol, sulfinalolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;
- Drugs for vascular disorders: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betaistine, brovincamine, bufeniode, citicoline, clobenfurool, clopidogrel, cyclandelate, heparine, dalteparin, dipiradamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, lamifiban, nadropanin, nicotinoyl alcohol, nyldrin, ozagrel, perhexiline, prenilamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinophedrine, tinzaparin, triflusal, xanthinol niacinate, fenilpropanolamine, midodrine;
- Antidiabetics: acarbose, carbutamide, glibornuride glybuthiazol, miglitol, repaglinide, troglitazone, 1-buthyl-3-methanyl-urea, tolrestat, nicotinamide;
- Antitumoral drugs: ancitabine, anthramicine, azacitidine, azaserine, 6-azauridi-

- ne, bicalutamide, carubicine, carzinophilin, chlorambucil, chlorozotocin, citarabine, daunorubicine, defosfamide, demecolcine, denopterine, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicine, droloxifene, edatrexate, eflornithine, enocitabine, epirubicine, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracyl, gemcitabine, hexestrol, idarubicine, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptapurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, micophenolic acid, ninopterine, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamicine, podofillic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, tiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicine;
- Antiulcer drugs:  $\epsilon$ -acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazol, ornoprostil, pantoprazol, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;
  - Antihyperlipidemic drugs: atorvastatine, cilastatine, dermostatine, fluvastatine, lovastatine, mevastatine, nistatine, pentostatine, pepstatine, privastatine sodium salt, simvastatine;
  - Antibacterial drugs: amdinocillin, amoxicillin, ampicillin, apalcillin, apicyclin, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazoline, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftazole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clofoctol, clometocilline, cloxacilline, cyclacilline, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, me-

clocycline, meropenem, metampicillin, metaciclone, meticillin sodium salt, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycine, novobiocin, oxacillin, pamipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, pheneticillin potassium salt, pipacicyne, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidine, argininsa, arbekacin, apramycin, amikacin, azithromycin, bacampicillin, cefcapene pivoxil, cefpodoxime proxetil dapsone, deoxydihydrostreptomycin dibekacin, etambutol, flumequine, guamecycline, nifurpirinol, nifurprazine, nitroxoline, glyconiazide, isoniazide, opiniazide, mupirocin, negamycin, netilmicin, pipacycline, fortimycins, gentamycin, ibostamycin, lincomycin, micronomycin, midecamycin, miokamycin, oleandomycin, paromomycin, rosaramycin, sisomycin, streptomycin, tobramycin, trospectomycin, claritromycin, diritromycin, enviomycin, erithromycin, josamycin, midecamycin, miocamycin, rifabutine, rifamide, rifamycin, rifaxymine, rokitamycin, spiramycin, troleandomycin, viomycin, virginiamycin; p-aminosalicylic acid, benzilpenicillinic acid, acetyl sulfametossipirazine, acediasulfone, 4-sulfanylamidosalicylic acid, 4,4'-sulfinyldianiline, 4'-(methylsulfamoyl)sulfanylanilide, 2-p-sulfanilylanilinoethanol, N-sulfanilyl-3,4-xylamide, p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, salazosulfadimidine, salinazid, succisulfone, sulfabenzamide, sulfacetamide, sulfachlorpiridazine, sulfachrysoidine, sulfacitine, sulfadiazine, sulfadicramide, sulfadimetoxine, sulfadoxine, sulfaetidol, sulfaguandine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfametazine, sulfametzol, sulfamethomidine, sulfametoxazol, sulfametoxypyridazine, sulfamethylthiazol, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanylamide, sulfanyllurea, sulfaperine, sulfafenazol, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfatiazol, sulfathiourea, sulfisomidine, sulfisoxazol, sultamicillin, tiazosulfone, mafenide, clofazimine, carbomycin, clomocycline, meclocycline, metampicillin, meticillin, metronidazole, mezlocillin, moxalactam, oxytetracycline, piromidic acid, pivampicillin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, grepafloxacin, lomefloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, rifanpin, rifloxacin, ta-

lampicillin, trovafloxacin, tosufloxacin, sparfloxacin;

- Antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxine, ribavirine, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;
- Inhibitors of bone reabsorption: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;
- Drugs for dementia: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

When the compounds include at least one asymmetric carbon atom, the products can be used in racemic mixture or in form of single enantiomer.

The active principle in the solid dispersions of the invention is in amorphous form. By "amorphous form" of a compound it is meant a solid form of that compound that when subjected to DSC analysis does not show the melting endothermic peak.

When the active principle is in the solid dispersions of the present invention it is characterized by a higher dissolution rate and therefore a higher bioavailability than in the non dispersed form. As it will be shown in detail in the following examples, a particularly high increase in the dissolution rate occurs when the hydrophilic polymer used in the dispersion is polyvinylpyrrolidone. Thus, the use of the polyvinylpyrrolidone as the hydrophilic polymer is particularly preferred when a very fast release of the active agent is desired.

Preferably the solid dispersions of the present invention comprise one or more nitrate active principles in amounts comprised between 5% and 60% w/w and preferably between 15% and 40% w/w and the hydrophilic polymer in amount ranging from 50% to 90%, preferably between 70% and 85% w/w.

Optionally, the solid dispersions of the present invention comprise also pharmaceutically acceptable excipients such as, for instance, wetting and solubilising agents in amount preferably ranging from 2% to 20%. Preferably the solubilising agents are surfactants, and among them most preferred are polysorbates, esters and ethers of polyethylen glycols, polihydroxylated castor oil and sodium laurylsul-

phate. The solid dispersion of the invention can be produced by using processes known in the art such as, for instance, the methods based on co-precipitation, the methods based on melting, which consist in melting together the active agent and the carrier and then cooling the melted mass, among them it is mentioned in particular "snap-cooling" where the cooling of the melted mass is carried out on stainless steel plates, "injection molding" where the molten mass is injected into a mould, hot melt extrusion where the active principles and the carrier mixture while flowing through the extruder is contemporaneously melted, homogenized and then extruded in the form of pellets, granules and other intermediates to be used for the production of tablets (the advantage of this technique is that the mixture is subjected to high temperatures just for one minute and it is therefore suitable for active agents sensible to high temperatures), "spray congealing", where cooling of the melted mass is carried out by freezing, and the methods based on solvent evaporation, consisting in dissolving the active agent and the carrier in the same solvent, or in forming an emulsion of the active agent and of the carrier in the solvent. Among these methods a technique allowing to easily and quickly obtain solid dispersions is "spray drying". An especially preferred process for the production of the solid dispersions of the invention is a spray-drying process comprising the following steps:

- a) dissolving the active principle in a solution or suspension of the hydrophilic polymer;
- b) spraying the mixture obtained in step (a) through the standard nozzle of a sprayer at a flow rate ranging from 5 to 60 ml/min and at a temperature of the inlet air comprised between 50°C and 130°C.

The solution or suspension of step a) can be realized in solvents such as, for instance, water, ethanol, isopropyl alcohol, methylen chloride, butanol, cyclohexane, hexane, acetone or mixture thereof. The choice of the solvent depends on the characteristics of solubility of the active agent which has to be dissolved.

The concentration of polyvinyl pyrrolidone, hydroxypropylmethylcellulose or polyethylene glycol in said solution or suspension is comprised between 1% and 10% w/v and preferably between 2.5% and 7.5% w/v.

The active principle ingredient is added to said solution or suspension in such an

amount to obtain a concentration comprised between 0.1% and 10% w/v and preferably between 0.5% and 7.5% w/v.

Optionally, at least one of the above mentioned pharmaceutically acceptable excipients can be added to the solution or suspension in such an amount as to obtain a concentration of said excipients comprised between 0.01% and 10% w/v and preferably between 0.05% and 5% w/v.

The spraying carried out in step b) is preferably carried out at a flow rate comprised between 5 and 60 ml/min and at an inlet air temperature comprised between 50°C and 130°C.

The solid dispersions of the present invention can be administrated as such, in form of powder, or used, for instance, for the production of granulates, tablets, capsules, suspensions, solutions, suppositories and aerosols.

Therefore, a further object of the present invention are pharmaceutical formulations for oral, parenteral, rectal, (trans)dermic or (trans)mucosal administration of the nitrate active principles comprising the solid dispersions of the invention.

If compared to conventional formulations, the formulations of the invention allow to improve the bioavailability and the onset of action of the nitrate active principles.

The invention will be now explained in detail by the following examples to be considered as a not limiting explanations of the invention.

#### EXAMPLE 1

##### Preparation of solid dispersions of the 4- acetylamino phenyl ester of the 4-nitroxybutanoic acid (NCX701).

A solution in methylene chloride/ethanol (90/10 v/v) including 0.8823% w/v of 4-acetylamino phenyl ester of the 4-nitroxybutanoic acid and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. This has then been sprayed through the standard nozzle (inner diameter 1 mm) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) at a flow rate of 20 ml/min while keeping an inlet hot air temperature of 60°C.

The obtained product has then been analysed by scanning calorimetry using a DSC T.A.2910 of T.A. INSTRUMENTS, with a heating interval and scanning rate of 10°C/min. under constant nitrogen flow. The obtained thermogram, reported in Figure 1, shows that the analysed product is amorphous. In fact no thermic event

is detected in the considered temperature interval and in particular in correspondence with the melting temperature of the 4-acetylamino phenyl ester of the 4 nitroxybutanoic acid, at 78°C.

## EXAMPLE 2

5 Evaluation of the dissolution rate of 4-acetylamino phenyl ester of 4 nitroxybutanoic acid in solid dispersion

The dissolution rate of the active principle of the solid dispersion produced in Example 1 has been evaluated, in comparison with the dissolution rate of the pure active principle in micronized form with the paddle method, described in F.U.X.,  
10 using the following conditions:

dissolution means: distilled water

temperature: 37°C±0.5

stirring rate: 100 r.p.m.

The quantity of active ingredient released has been evaluated by UV spectrophotometry at a wavelength of 240 nm. The following table shows the average of the  
15 results obtained from three determinations, expressed as percentage of active principle dissolved at different time intervals:



TIME (minutes)	Micronized active principle	Solid dispersion
5	17.8	100
10	38.8	100
15	52.1	100
20	60.7	100
25	67.5	100
30	72.4	100
35	76.4	100
40	79.7	100
45	82.6	100
50	85.2	100
55	87.3	100
60	94.9	100

As it can be observed from the table, while the active principle as such is characterized by a slow dissolution in water, when this is in the form of a solid dispersion in polyvinyl pyrrolidone its dissolution is immediate, occurring in less than five minutes.

### EXAMPLE 3

Preparation of solid dispersions of 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid (NCX4016)

Two solutions in methylene chloride/ethanol (90/10 v/v) having the following compositions have been prepared:

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of polyvinyl pyrrolidone K25;

2.1 % w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/p of polyvinyl pyrrolidone K25;

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of hydroxypropylmethylcellulose.

- 5 The solutions have then been sprayed as described in Example 1. The product obtained has been analysed by scanning calorimetry using a device described in the preceding example. The thermogram obtained, reported in Figure 2, shows that the analysed product is amorphous. In fact no thermic event is detected in the considered temperature interval and in particular in correspondance with the  
10 melting temperature of the 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid, at 63.52°C.

#### EXAMPLE 4

##### Determination of the dissolution rate of NCX4016 in solid dispersion

- The dissolution rate of the solid dispersion produced in the example 3 has been  
15 compared with the dissolution rate of the pure NCX4016 in micronised form using the paddle method described in F.U.X., according to the following operating conditions  $T = 37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ , stirring rate: 150 rpm, dissolution means: 1% sodium lauryl sulphate solution, dissolution volume: 900 ml.

- The quantity of NCX4016 released has been spectrophotometrically evaluated in  
20 continuous at a wavelength 232 nm. The following table shows the average of the results obtained from 3 determinations, expressed as percentage of active principle dissolved at different time intervals.

TIME (minutes)	NCX4016 micronized	NCX4016 Solid dispersion 1	NCX4016 Solid dispersion 2	NCX4016 Solid dispersion 3
5	17.9	98.2	98.1	27.3
10	39.2	99.9	99.2	65.7
15	53.5	100	100	81.1
20	60.7	100	100	90.2
25	71.4	100	100	92.4
30	77	100	100	94.1
35	80.9	100	100	94.7
40	84.4	100	100	94.9
45	87	100	100	95.4
50	88.9	100	100	95.4
55	90.6	100	100	95.4
60	91.4	100	100	95.4

Also in this case, as it can be observed from the table, the dissolution rate of the active principle in all the three solid dispersions is higher than that of the active principle in pure form. Moreover, when the active principle is dispersed in polyvinyl pyrrolidone, the increase in the dissolution rate is remarkably high and an almost immediate release is observed.

#### EXAMPLE 5

Evaluation of the dissolution rate of 3-(nitroxymethyl)phenyl ester of the 2-acetoxybenzoic acid (NCX4016) in solid dispersion under condition of supersaturation

Three samples of microspheres have been exactly weighed so as to have a con-

tent of nitroaspirine of 30 mg. This quantity corresponds to about 4 times the solubility in water of the active principle.

The dissolution rate of the active principle from the above mentioned 3 solid dispersions has been compared with the dissolution rate of the pure active principle  
5 in micronized form, with the paddle method, described in F.U.X. using the following conditions:

dissolution means: distilled water

temperature:  $37^{\circ}\text{C} \pm 0.5$

stirring rate: 100 r.p.m.

10 volume = 900 ml

The quantity of NCX 4016 released has been evaluated spectrophotometrically in continuous at a wavelength 232 nm.

The samples have been taken by means of a peristaltic pump at 5 minutes intervals and for the total time of one hour.

15 The following table shows the average of the results obtained from three determinations, expressed as percentage of dissolved active principle at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion 2
5	n.r. <sup>a</sup>	55.1
10	n.r. <sup>a</sup>	54.3
15	n.r. <sup>a</sup>	51.8
20	n.r. <sup>a</sup>	48.7
25	n.r.	46.9
30	Nr. <sup>a</sup>	44.7
35	n.r. <sup>a</sup>	42.8
40	n.r. <sup>a</sup>	40.8
45	n.r. <sup>a</sup>	38.6
50	n.r. <sup>a</sup>	37.3
55	n.r. <sup>a</sup>	35.7
60	n.r. <sup>a</sup>	34.3

a: spectrophotometrically not detectable

The quantity of active agent NCX4016 dissolved after 5 minutes is about twice the solubility of the active ingredient in the dissolution means.

#### 5 EXAMPLE 6

Preparation of solid dispersions of HCT 1026 (2-fluoro- $\alpha$ -methyl[1,1'-biphenyl]4-acetic acid-4nitrooxy butyl ester

Two solutions in methylene chloride/ethanol (90/10 v/v) with the following compositions have been prepared:

10 HCT 1026 0.44% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

HCT 1026 0.88% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

The solutions have then been sprayed under the same conditions used in Example 1.

**EXAMPLE 7****Evaluation of the dissolution rate of the HTC1026 in solid dispersion**

The dissolution rate of the HCT 1026 from the solid dispersion 1 has been evaluated, in comparison with the dissolution rate of the pure active ingredient, with the paddle method described in F.U.X. In detail, 50 mg of the solid dispersion 1 and 7.5 mg of pure active ingredient are placed in a thermostatic container at 37°C±0.5°C in 900 ml of distilled water including 1% w/v of SDS and kept under stirring at 150 rpm. The quantity of HCT 1026 passed into the solution is continuously spectrophotometrically determined in continuous at a wavelength of 245 nm.

In the following table the average of the results obtained from three determinations is reported, expressed as percentage of active principle dissolved at different time intervals:

TIME (minutes)	Pure HCT 1026	Solid dispersion 1
5	5.84	81.04
10	16.74	84.74
15	23.6	85.2
20	29.84	86.13
25	32.78	85.67
30	37.92	85.85
35	42.57	86.31
40	47.46	86.68
45	54.94	86.78
50	58.98	86.78
55	58.98	87.42
60	64.72	87.79

The results obtained show also in this case that when the active agent is in solid dispersion in polyvinyl pyrrolidone its dissolution speed is much higher than the one of the active agent in non dispersed form, and the release of more than 80% of the active principle is observed in less than 5 minutes.

#### 5 EXAMPLE 8

##### Preparation of solid dispersions of NCX 1022 (hydroxycortisone 21-[(4'-nitroxy-methyl)benzoate]

A solution of methylene chloride/ethanol (90/10 v/v) including 0.44% w/v of NCX 1022 and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. It has then  
10 been sprayed through the standard nozzle (1 mm inner diameter) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow rate of 20 ml/min keeping a temperature of the inlet hot air of 60°C.

The product obtained has then been analyzed through scanning calorimetry by using the device described in the preceding examples. The thermogram obtained,  
15 reported in Figure 3, shows that the analysed product is amorphous and degrades at a temperature lower than 200°C. In fact no thermic event is detected in the considered interval of temperature and in particular in correspondance with the melting temperature of the NCX 1022.

#### EXAMPLE 9

##### 20 Determination of the dissolution speed of the solid dispersion of NCX 1022

The dissolution rate of the active ingredient from the solid dispersion produced in Example 6 has been compared with the dissolution rate of the pure active ingredient, using the paddle method described in F.U.X. In detail, 40 mg of the solid dispersion or 5 mg of pure NCX 1022 have been placed in a thermostated container  
25 at 37°C±0.5°C in 500 ml of distilled water including 1% w/v of Tween 80 and kept under stirring at 100 rpm. The quantity of NCX 1022 dissolved has been spectrophotometrically determined in continuous at a wavelength of 240 nm:

The following table shows the average of the results obtained from three determinations, expressed as percentage of ingredient dissolved at different time intervals:  
30

TIME (minutes)	Micronized active principle	Solid dispersion
5	4.05	45.56
10	3.91	49.73
15	3.86	50.36
20	3.81	49.90
25	3.91	48.84
30	3.77	47.18
35	3.91	45.60
40	3.77	43.71
45	4.09	41.93
50	4.33	40.2
55	4.23	38.82
60	4.32	37.18

The results obtained show that, even if the solubility of the pure active principle almost null, with a solubilisation of only 4.3% within one hour, when this is in form of a solid dispersion in polyvinyl pyrrolidone its dissolution rate and therefore its apparent solubility remarkably increase and it is possible to obtain the release of 50% of active ingredient in less than 15 minutes.

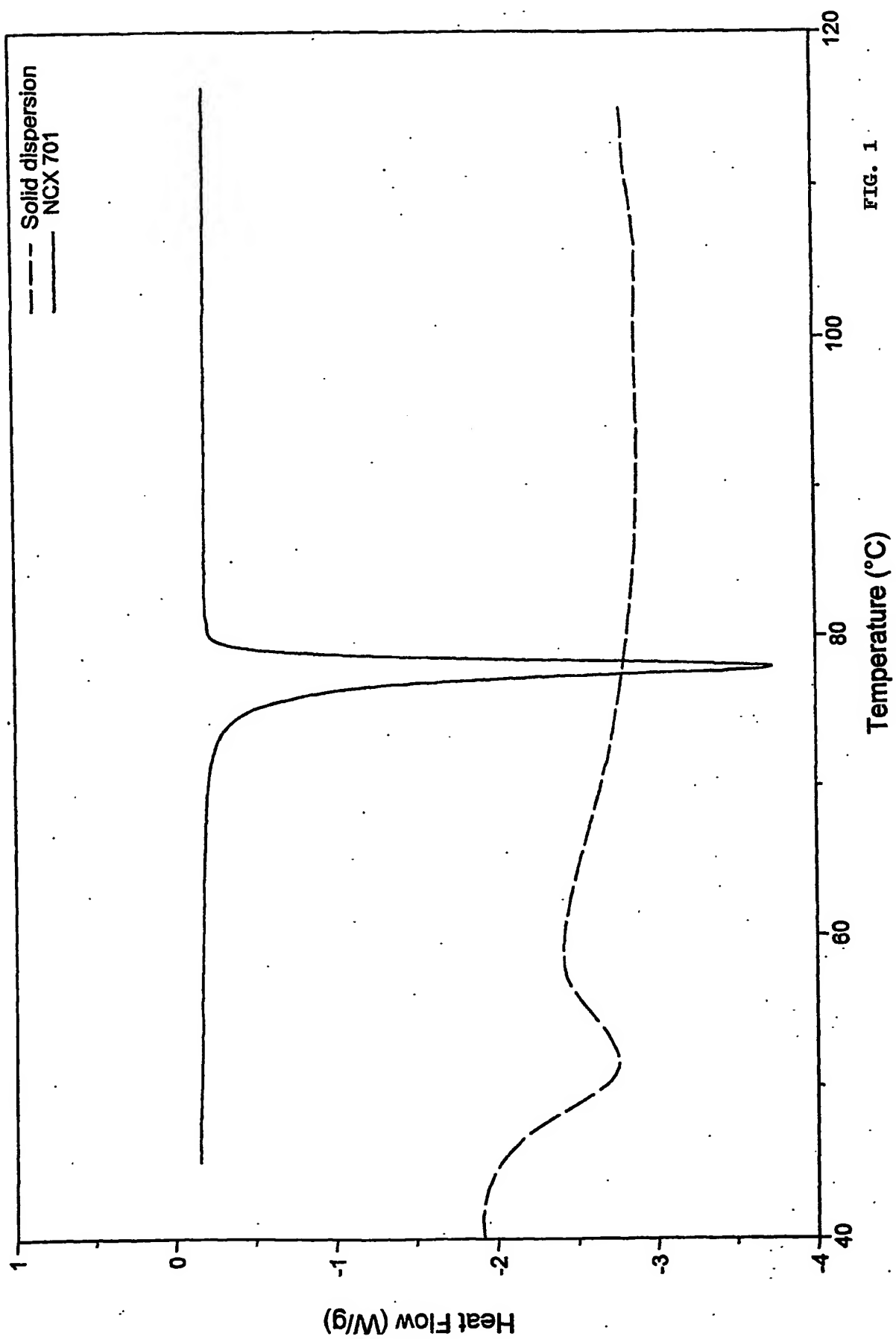


**CLAIMS**

1. Solid dispersions comprising at least one nitrate active ingredient and one hydrophilic polymer chosen among cellulose ether, polyvinyl pyrrolidone, polyethylene glycol.
- 5 2. Dispersions according to claim 1 wherein said polymer is polyvinyl pyrrolidone .
3. Dispersions according to claim 1 wherein said cellulose ether is hydroxypropylmethylcellulose and it has a molecular weight such that the viscosity at 20°C of a 2% solution in water is lower than 50 cps.
4. Dispersions according to claim 1 wherein polyvinyl pyrrolidone has an average  
10 molecular weight comprised between the molecular weight of polyvinyl pyrrolidone K17 and the molecular weight of polyvinyl pyrrolidone K30.
5. Dispersions according to claim 1 wherein polyethylene glycol has an average molecular weight higher than or equal to the molecular weight of polyethylene glycol 1000.
- 15 6. Dispersions according to claim 1 wherein said active ingredient is contained in amounts ranging from 10% to 50% w/w and said hydrophilic polymer is contained in amounts ranging from 50% to 90%.
7. Dispersions according to claim 6 wherein the amount of said active ingredient is between 15% and 40% w/w.
- 20 8. Dispersions according to claim 6 wherein the amount of said hydrophilic polymer is between 60% and 85%.
9. Dispersions according to claim 1 further comprising pharmaceutically acceptable excipients.
10. Dispersions according to claim 9 wherein said excipients are contained  
25 amounts comprised between 2% and 20%.
11. Dispersions according to claim 9 wherein said pharmaceutically acceptable excipients are chosen from the group consisting of wetting and solubilising agents.
12. Dispersions according to claim 11 wherein said solubilising agents are surfactants.
- 30 13. Dispersions according to claim 12 wherein said surfactants are chosen from the group comprising polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodiumlauryl sulphate.

14. Pharmaceutical formulations for oral, rectal, parenteral, transcutaneous, transmucosal administration of active principles comprising the solid dispersions according to claims 1 to 13.

1/3



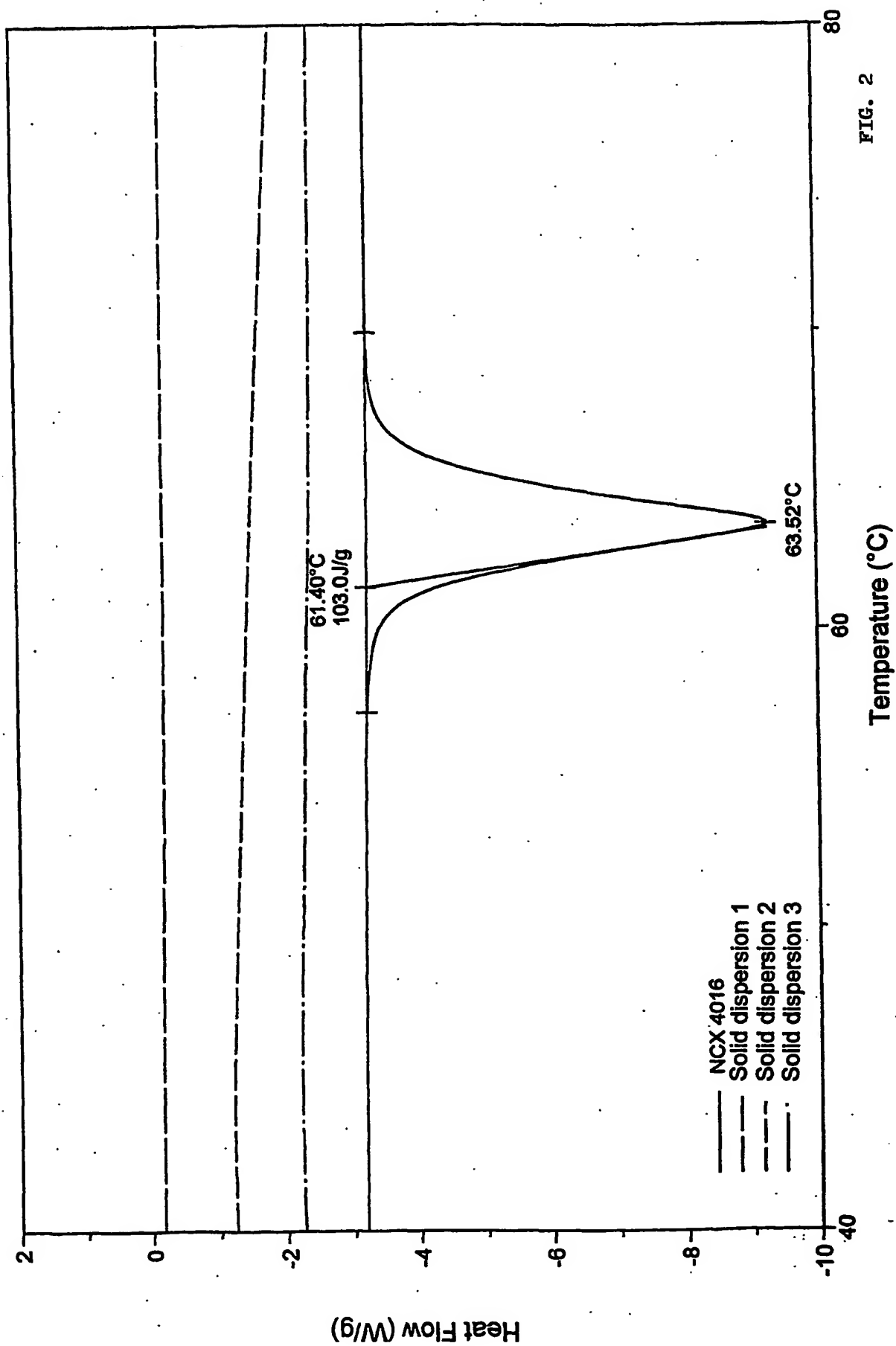
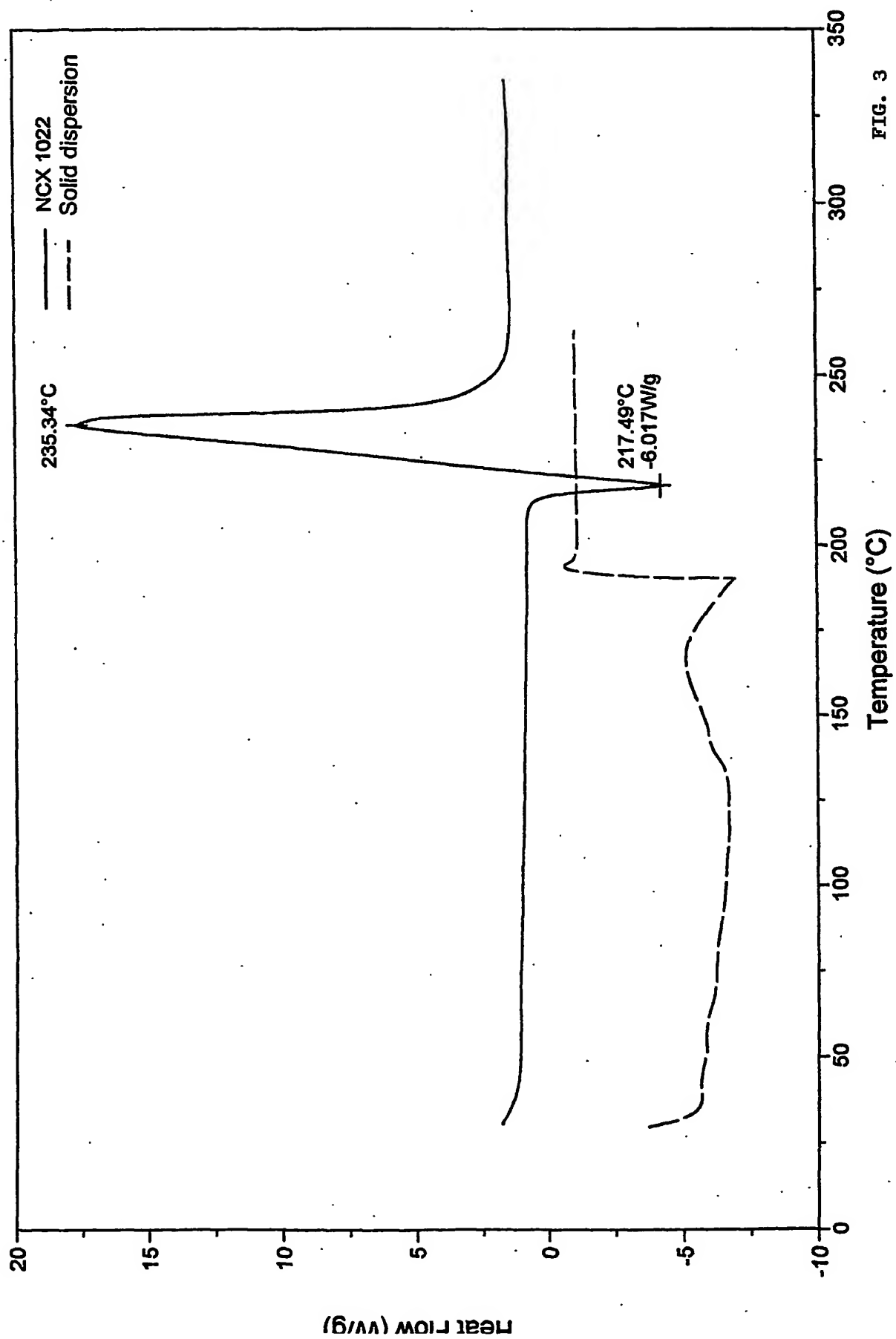


FIG. 2



## INTERNATIONAL SEARCH REPORT

 Application No  
 PCT/EP 01/14967

 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINGHETTI, P.; ET AL.: "Application of solubility parameter in nitroflurbiprofen topical semisolid formulations" PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 27TH, 7 - 13 July 2000, pages 936-937, XP002199487 Paris (FR)	1,5,9,14
Y	page 936; example 2; table 1	1
P,Y	WO 01 15677 A (ALCON LABORATORIES) 8 March 2001 (2001-03-08) claims 1,7,10,11 page 10, line 6 - line 17 page 14, line 1 - line 8	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

21 May 2002

Date of mailing of the international search report

06/06/2002

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Ventura Amat, A

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14967

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0115677	A	08-03-2001	AU	6917400 A	26-03-2001
			WO	0115677 A2	08-03-2001

---